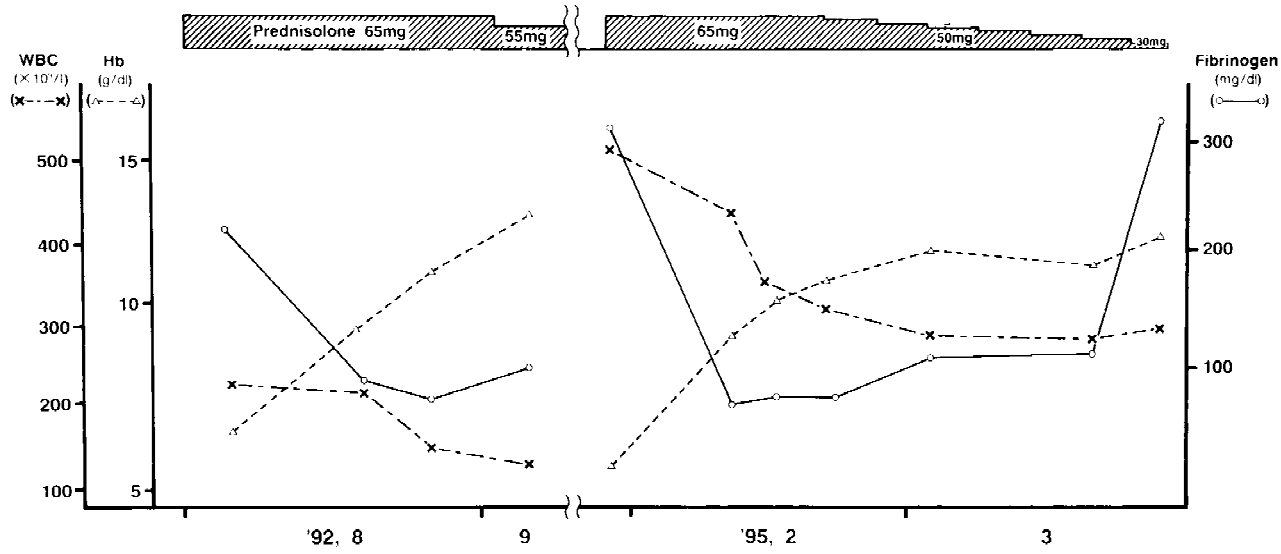

Fig. 1. Clinical course of patient. Shaded column at top shows dose of prednisolone. Dose of prednisolone was tapered from September 1992, and was 5 mg/day in January 1995 when the AIHA relapsed. Fibrinogen values determined by thrombin time method are shown.

day (65 mg/day)). After starting this therapy, the plasma fibrinogen level promptly decreased (Fig. 1). There was no clinical or laboratory evidence of disseminated intravascular coagulation (DIC) or liver disease. Further evaluation and follow-up study of the hypofibrinogenemia were not done at this time. In January 1995, when he received 5 mg of PSL, the AIHA relapsed. The laboratory findings were: white blood cells (WBC) 496.0 × 10^9/l (99.5% CLL cells), hemoglobin (Hb) 5.4 g/dl, reticulocytes 221.3 × 10^9/l, platelets 192 × 10^9/l, alanine aminotransferase 11 IU/l, lactate dehydrogenase 1,938 IU/l, indirect bilirubin 1.9 mg/dl, total protein 6.4 g/dl, albumin 4.3 g/dl, total cholesterol 171 mg/dl, haptoglobin 8.8 mg/dl (normal range, 41–318), and plasma fibrinogen 334 mg/dl (normal range, 200–400). DIC was not observed. He was given 65 mg/day of PSL again. Two weeks later, the plasma fibrinogen level decreased to 84 mg/dl. Both the thrombin time method and single radial immunodiffusion method showed similar low plasma fibrinogen values. Other coagulation studies were performed repeatedly, including the prothrombin time, activated partial thromboplastin time, hepaplastin time, plasma levels of factors VII and X, fibrin/fibrinogen degradation products, D-dimer, thrombin-anti-thrombin III complex, alpha 2-plasmin inhibitor-plasmin complex, fibrinopeptide A, and fibrin monomer complex; all showed normal values. After the anemia improved, the dose of PSL was gradually reduced. The plasma fibrinogen level did not return to normal until the dose of PSL was reduced to 30 mg/day (Fig. 1). There was no bleeding complication throughout the clinical course.

This case had no known causes of acquired hypofibrinogenemia (i.e., DIC, liver disease, or administration of drugs that impair protein synthesis in the liver, such as L-asparaginase, or that accelerate fibrinolysis), and the development of hypofibrinogenemia twice coincided with the use of PSL. The literature includes rare cases in which combination drug therapy containing a glucocorticoid induced hypofibrinogenemia [1–5]; most of these cases had lymphoid malignancies.

Therefore, it is highly likely that PSL induced the hypofibrinogenemia in this case. It is also possible that the malignant lymphoid cells played a role in the development of hypofibrinogenemia. In this case, it seems unlikely that the subclinical DIC or primary hyperfibrinogenolysis was induced by an unknown protease released from the CLL cells because all of the sensitive markers for DIC and primary fibrinogenolysis showed normal values. Fibrinogen is synthesized in the liver, is distributed mainly in the plasma, interstitial fluid, and lymph, and is catabolized by unknown mechanisms. Glucocorticoids may alter some step(s) in fibrinogen kinetics.

We suggest that glucocorticoids should be considered as a cause of acquired hypofibrinogenemia, especially in cases of lymphoid malignancy.

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Anti-Phospholipid-Antibody Syndrome Associated With Peripheral T-Cell Lymphoma

To the Editor: Peripheral T-cell lymphomas (PTCL) include heterogeneous diseases, among which only angioimmunoblastic T-cell lymphoma, angiocentric lymphoma, intestinal T-cell lymphoma, and adult T-cell lymphoma/leukemia can be considered distinct entities. The remainder, constituting

TABLE I. Results of Laboratory Evaluation

Laboratory evaluation	
Hemoglobin	114 g/l
White blood cell count	13.2 × 10^9/l
Neutrophils	51%
Lymphocytes	14%
Blasts	27%
Platelets	610 × 10^9/l
Sedimentation rate	71 mm/hr
C-reactive protein	153 mg/l
LDH	626 U/l
β2-microglobulin	3.05 mg/l
Anti-HIV	Negative
Anti-HTLV 1/2	Negative
Anti-nuclear antibodies	Positive, 1:40
Immunophenotype of circulating blasts	CD4+, CD3−, CD2−, CD8−, CD7−, CD19−, CD14−
Rearrangement of T-cell receptors	Negative
Cytogenetic study	No chromosome abnormalities
Coagulation studies	
Fibrinogen	529 mg/dl
Fibrin split products	57.04 μg/ml
Lupus anticoagulant	Positive
Anti-cardiolipin IgG	14 units/ml (N = 0–15)
Anti-cardiolipin IgM	22 units/ml (N = 0–12.5)
Prothrombin time	Normal
Partial thromboplastin time	Normal
Protein C	Normal
Protein S	Normal
Plasminogen	Normal
Heparin cofactor	Normal
Antithrombin III	Normal

the majority of cases of PTCL, are grouped in the provisional category of ''peripheral T-cell lymphoma, unspecified.'' They are characterized morphologically by a usually diffuse proliferation of heterogeneous cells with a broad spectrum of cell sizes. CD4 is more commonly expressed than CD8, and T-cell receptor genes are usually rearranged. They usually affect adults, with generalized disease that may involve extranodal sites. Their clinical course is variable but often aggressive and with frequent relapses [1,2].

The main clinical features of anti-phospholipid-antibody syndrome (APS) are venous and arterial thrombosis, neuropsychiatric disorders, thrombocytopenia, and recurrent spontaneous abortion. The serologic markers of the syndrome are anti-cardiolipin antibodies and the lupus anticoagulant [3]. APS often occurs in systemic lupus erythematosus or related autoimmune diseases. Anti-phospholipid antibodies (aPL) have been reported in association with neoplastic disease and lymphoproliferative disorders [4,5].

A 65-year-old man with a history of hypertension and ischemic stroke was admitted because of relapsing deep-venous thrombosis. Physical examination revealed bilateral axillary lymphadenopathy, mild splenomegaly, and signs of thrombophlebitis of the left lower limb. Table I shows the results of laboratory evaluation.

Bone-marrow biopsy showed involvement by lymphoma. Biopsy of an axillary lymph node yielded a diagnosis of PTCL of unspecified type, according to the R.E.A.L. classification [1], with predominant medium-sized cells (diffuse mixed small- and large-cell lymphoma, intermediate grade F according to the Working Formulation) [6]. B-mode venous ultrasonography plus Doppler was consistent with left iliac, femoral, and popliteal deep-venous thrombosis. A total-body CT scan found mediastinal lymphadenopathy, moderate splenomegaly, partial thrombotic obliteration of the main branches of the pulmonary artery, and a possible left renal infarct. Brain CT scanning, performed following a transitory ischaemic attack (TIA) with transitory aphasia, confirmed multiple diffuse ischemic lesions.

Treatment with intravenous heparin followed by oral warfarin led to regression of the left lower limb deep-venous thrombosis. Monochemotherapy for lymphoma with chlorambucil was begun on account of the limited extension of disease, the patient's age, the tendency for frequent relapses of peripheral T-cell lymphoma, and the immunosuppressive action of the drug.

Various autoantibodies can be found in the serum of patients with hematological malignancies. The presence of aPL in patients with non-Hodgkin's lymphoma and acute myeloid leukemia has been reported in a few cases [4,5]. It has also been suggested that these autoantibodies may have a role as markers of disease activity and progression in some hematological malignancies [5]. The patient described here had a PTCL in association with an overt clinical course of APS.

The nature of the association between lymphoproliferative disease and APS needs to be established, but it does not seem likely to be merely casual. Possible pathogenic mechanisms may involve the secretion of cytokines by malignant T cells, activating the B-cell compartment to produce aPL. Thrombocytosis and the high level of C-reactive protein found in this patient might indicate expression of increased production of cytokines such as IL6.

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